REMARKS

Applicant's representative conducted a phone interview with the Examiner and SPE on June 29, 2007. The topics discussed were establishing date of invention before the effective date of prior art references, the non-enablement rejection and the restriction of claims. Both the Examiner and SPE were extremely helpful in clarifying the issues and those efforts are appreciated.

Claims 1-22 were pending in the application. Claims 8-22 were withdrawn from consideration, claims 1-7 were rejected and claim 1 was objected to. Claims 2 and 8-22 are herein canceled, claim 1 is amended and claim 23 is new. None of the amended or new claims introduce new subject matter. Amended claim 1 incorporates the limitation of canceled claim 2 and is otherwise supported in the specification at page 1, lines 9-10, and page 9, lines 8-10. New claim 23 is supported at page 11, lines 29-31.

Claim Objections

Claim 1 was objected to because of claiming informalities. The amendment to claim 1 corrects the informality.

35 USC § 112

Claims 1-7 were rejected under 35 U.S.C. § 112, first paragraph, for nonenablement because the specification, while being enabling for treating the incidence of diabetes mellitus in a subject with chronic heart failure, is allegedly not enabling for preventing diabetes mellitus.

Claim 1, as amended, now recites that it is a method for lowering the incidence of onset of diabetes mellitus in a non-diabetic subject with chronic heart failure. Thus the language that the Examiner found to be problematic is no longer in the claim. It is believed that the currently claimed invention is supported by disclosure in the specification that enables one skilled in the art of the invention to practice the inventive method.

The nature of the invention is basic: administering ACE-inhibitor lowers the incidence of onset of diabetes mellitus in nondiabetic patients with chronic heart failure and impaired FPG. The complexity of the invention was in the interpretation of the clinical trial data to conceive of the present invention, rather than in the practice of the method. Since the relative skill of those in the art is high (Ph.D. and M.D. level), those skilled in the art can comprehend the specification

as the data is presented and can comprehend the methods of correlating the data to the problem at hand.

The breadth of the current claims is limited. The method is applied to non-diabetic subjects with chronic heart failure and impaired fasting plasma glucose. Thus, the Examiner's concern with how this method prevents type 1 diabetes which occurs in childhood and adolescence is not relevant to the amended wording of the claim. Not all subjects are contemplated by this invention. Subjects with chronic heart failure and impaired FPG are contemplated.

Guidance of the Specification is sufficient, considering that the relative skill of those in the art is high. The guidance needed to achieve the claimed method is given, i.e., administer a therapeutically effective amount of an ACE inhibitor to the patient, and check for onset of diabetes. The specification relates the reference citation for the SOLVD studies in which ACE inhibitor was administered to patients. Since the methods for administration are known in the art, and methods to check for onset of diabetes are known in the art, the guidance is sufficient.

Working Examples. What is presented here is an analysis of data collected from a multicenter and multiple clinical trials study of the effect of ACE inhibitor on survival in patients with left ventricular dysfunction. The Examiner conceded that working examples are provided that are directed toward treatment (i.e. administering an ACE inhibitor to a non-diabetic pateient with chronic heart failure, with or without impaired FPG.

The specification describes a working example of a treatment that statistically prevented the onset of diabetes mellitus in patients without diabetes who had chronic heart failure (See the study at page 5, line 15 through page 9, line 10). This is clearly stated in the discussion of the results at page 9, lines 8-10 and shown by the evidence provided in the study.

Predictability of the Art. The Examiner's discussion on the predictability of the art appears to be focused solely on the whether intervention with ACE inhibitors affects the heart defect. This discussion is not relevant to the instant rejection for non-enablement because the topic here is whether the method for lowering the incidence of onset of diabetes is enabled. The Examiner did not discuss diabetes. Therefore, it is respectfully asserted that this element of the grounds for the rejection does not support the rejection.

It appears that the Examiner's conclusion of nonenablement was based on an incorrect analysis of the multiple factors of the Wands test. The analysis indicates some confusion about the description of the clinical trials on heart disease and the subsequent analysis of data from that SOLVD multicenter clinical trial study of heart disease. While the clinical trials were directed to a study of treating or preventing heart disease by administering an ACE inhibitor, the important focus, in this patent application is that the subsequent analysis of the data from that study revealed surprising insights that ACE inhibitors can prevent the onset of diabetes mellitus. Although the clinical trials were not directed to treating or preventing diabetes, the inventors were able to make insightful correlations to diabetes by using data collected in the follow-up visits which reported fasting plasma glucose (FPG) levels. The inventors diagnosed new onset diabetes according to criteria put forth by the American Diabetes Association as FPG $\geq$ 126 mg/dL at two different follow-up visits.

35 USC § 102

Claims 1-7 were rejected under 35 U.S.C. 102(a) as being anticipated by Vermes et al., Circulation 2003, 107:1291-1296, (February 17).

Applicant herein submits a Declaration of the inventors under 37 CFR 1.131 which provides factual evidence that the inventors conceived of the invention prior to the publication date of Vermes et al., and used due diligence to cause the filing of a provisional patent application describing the invention. Therefore, the publication should be removed as prior art.

Claims 1, 5, and 6 were rejected under 35 USC 102 (b) as anticipated by Yusuf et al. (JAMA, 2001; 286(15):1882-1885). Applicant traverses the rejection.

The claimed invention is a method for lowering the incidence of the onset of diabetes mellitus in a non-diabetic subject with chronic heart failure. The Yusuf study explicitly excludes subjects with chronic heart failure. In the Methods section, first paragraph, Yusuf et al. states that the trial was directed to individuals with *no evidence of left ventricular dysfunction or heart failure*. Thus, Yusef et al. does not anticipate the claimed invention.

35 USC § 103

Claims 1-7 were rejected under 35 U.S.C. 103(a) as being unpatentable over Knight et al. (Amer. Heart J. 1999; 138:849-855) taken with Bauters et al. (Cardiovascular Diab. 2003, 2:1-16) and Pan (US 5,130333). Applicant traverses the rejection.

The Declaration under 37 CFR 1.131, described above, removes the Bauters et al. publication as prior art. Notwithstanding, the removal of Bauters as prior art, Applicant makes the following further rebuttal argument.

In order to make a *prima facie* showing of obviousness, it is incumbent on the examiner to analyze the invention and the prior art in the manner outlined in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). The Examiner has failed to do so. Particularly, *Graham* necessitates a three-part analysis in which the scope and content of the prior art are determined, differences between the prior art and the claims at issue are ascertained, and the level of ordinary skill in the pertinent art is resolved. (*Id.* at 17-18). The Examiner has failed to examine the last two of the three prongs of the *Graham* analysis. This failure is sufficient reason to assert that there has been no *prima facie* showing of unpatentability. For this reason, Applicants respectfully request that the rejection of the claims be reconsidered and withdrawn.

Notwithstanding that in light of the failure to make a *prima facie* showing of obviousness the burden does not shift to the applicant to rebut an obviousness rejection, Applicant makes the following observations about additional failures in the Examiner's obviousness analysis.

The analysis of the Knight et al. reference contained misstatements of fact (Office Action, page 8, first paragraph). Contrary to the statement in the office action, the reference does not teach administering ACE inhibitors in order to reduce renal function in patients. The Knight et al. reference concerns the SOLVD study wherein either enalapril or placebo was administered to subjects with congestive heart failure (CHF) to determine whether enalapril was an effective treatment for CHF (Knight at p. 851, left col., first para.). Retrospectively, Knight et al. examined the data and concluded that administration of enalapril to patients with CHF *increased the risk of impaired renal function.* This teaching by Knight et al. is not relevant to the current patentability analysis because there is no claim made in the instant application directed to renal function.

Knight et al. also concluded that if the CHF subject also had diabetes, the risk of impaired renal function was less in the enalapril group than in the placebo group. This is not a statement that there is a reduction in risk with enalapril administration; but that the increased risk of impaired renal function was not as high with enalapril as with placebo. Most importantly, this last conclusion about diabetic subjects is not relevant to the instant method claims, because the claimed method is not directed to subjects who already have diabetes, the claimed method is directed to lowering the incidence of the *onset* of diabetes mellitus in non-diabetic subjects.

A further misstatement of fact is at Office Action page 8, last paragraph. The Examiner's analysis describes a motivation to combine the prior art to "administer enalapril an ACE inhibitor to inhibit the incidence of diabetes mellitus in a subject with chronic heart failure because the prior art teaches so...." Nowhere did the Examiner show that the prior art teaches that enalapril inhibits the incidence of diabetes mellitus in a CHF subject. Thus there is no rational basis for the Examiner's reliance on this statement as a motivation to combine the prior art. Apparently, the Examiner mistakenly has taken the disclosure of the application itself, and attributed it to the prior art. As such, the combination of the prior art is without rational grounds and for this reason, no *prima facie* showing of obviousness has been made.

Another misinterpretation of the prior art is evident in the description of motivation to combine at page 8 last paragraph of the Office Action which states, "diabetes mellitus is prevalent in heart failures as taught by Bauters et al. (see abstract)." Actually, the teaching by Bauters, is more particularly explained in the immediately following sentence of the Bauters Abstract, "Epidemiological studies have demonstrated an increased risk of heart failure in diabetics" and "Subgroup analyses of randomized trials demonstrate that diabetes is also an important prognostic factor in heart failure." Thus, the Bauters' teaching is that the occurrence of diabetes increases the incidence of heart failure, not the other way around. In respect of the actual meaning of Bauters, this reference does not serve to motivate one of ordinary skill in the art to make any judgements about whether a diagnoses of congestive heart failure has any prognosticative indication as to whether diabetes will ensue.

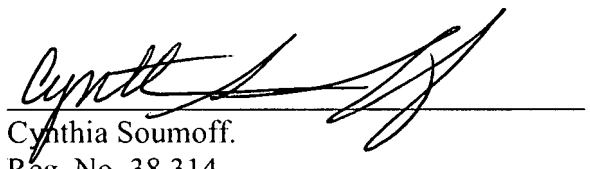
In respect of the discussion of the failures of the obviousness analysis, the Examiner has not provided a rational basis to show why one of ordinary skill would have combined the prior art. The U.S. Supreme Court has held that: "Rejections on obviousness cannot be sustained by

mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 2007, slip op. at page 14. In light of the absence any rational underpinning to support the legal conclusion of obviousness, the rejection cannot stand. For this reason, as well, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

In view of the foregoing, Applicants submit that all pending claims are in condition for allowance and request that all claims be allowed. The Examiner is invited to contact the undersigned should he believe that this would expedite prosecution of this application. It is believed that no fee is required. The Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 13-2165.

Respectfully submitted,

Dated: September 19, 2007



Cynthia Soumoff.
Reg. No. 38,314
Attorney for Applicant

MATHEWS, SHEPHERD, McKAY & BRUNEAU, P.A.
29 Thanet Road, Suite 201
Princeton, NJ 08540
Tel: 609 924 8555
Fax: 609 924 3036